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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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05/29/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/776,037	YOCK ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 November 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-104* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-104* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action replaces that action mailed 2/23/09, which is replaced in its entirety with the action herein. This action clarifies that the previously indicted allowed claims are not allowed.

This office action is in response to an amendment filed 11/20/08. Claims 1-104 are pending.

Upon further review of the instant claims and specification it is apparent that the claims indicated as allowed in the office action mailed 6/24/08 as well as the remainder of the claims are not in condition for allowance.

Furthermore, due to conflicting advice given on the format required for claim amendment, clarification is herein provided. Status identifiers for claims 20-104, newly added in the reissue, should be "new". However, it is noted that status identifiers are not required in reissue. As well, contrary to recommendations previously made, any deletions made should be indicated by single brackets regardless of the size of the deletion. In the interest of compact prosecution the instant claims will be considered in their current state.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
It does not identify the mailing address of each inventor. A mailing address is an address at which an inventor customarily receives his or her mail and may be either a home or business address. The mailing address should include the ZIP Code designation. The mailing address may be provided in an application data sheet or a supplemental oath or declaration. See 37 CFR 1.63(c) and 37 CFR 1.76. Specifically, the mailing address of Peter Fitzgerald is missing

Response to Amendment

Applicants' intent to send a new oath is acknowledged

Claim Objections

Claims 1, 3, 4, 7, 8, 9, 11, 13-17, 19, 31, 34, 36, 37, 39, 40, 41, 43-45, 47, 49, 50-53, 55-58, 60, 62, 66-69, 71, 73, 77, 78, 80, 81, 83, 85, 89, 90, 92, 96 and 100 are objected to because of the following informalities: Claims 1, 8, 15, 37, 44, 51, 56, 67, 78, 90 and 92 recite "A method of locally administrating an active agent to a host". It is noted that the claims recite a step of "administrating" which should more correctly be --administering--. Secondly, the claim recites that the agent is "locally" administered but does not indicate to where it is locally administered. A recommendation is that the claim be amended to recite --A method of locally administering an active agent *to a target site* within a host-- (emphasis added). Subsequent amendments to coincide with this should be made (based upon claim 1) to recite in line 3, --into a vascular vessel proximal to the target site-- and in line 6 , -- an adjacent interstitial place-- as opposed to "an interstitial place". Finally, the last line can recite, --said agent is locally administered to said target site--.

Furthermore, in claims 1, 8, 15, 56, 67 clarification would be provided by amending the claims to recite in lines 3 instead of "said agent", --said method comprising retroinfusing a

flowable formulation of said agent or a fluid delivery vehicle thereof into a vascular vessel (vein) of said host (with a catheter) under conditions to produce --.

Furthermore, in claims 1, 8, 15 and 56 it is grammatically clearer to recite --wherein [and for] said agent [to enter an] enters--. Similarly, in claims 37, 44, 51 the recitation "and infusing said agent" suggests the hand of man is "infusing". It would be clearer to recite --wherein said agent infuses an-- amd in claim 51 the following amendment is recommended, --to produce disruptive passageways thereof wherein said agent infuses--. Similarly, claim 67 (and claim 78 and 90), line 6-7 should be amended to --and under conditions that facilitate the transport of said agent--.

Claim 3 and 39 recite "said retroinfusing comprises providing stress". The specification teaches that stress is produced in the vessel by applying pressure or by application of energy or by application of chemical stress. As claim 1 is drawn to application of pressure, it appears as if the claim intends that a secondary or additional stress is applied see i.e. claim 5, 7 or 29. Thus, it would be remedial to recite, --said retroinfusion comprises application of an additional stress to the wall of said vessel--.

In claims 4 and 40, the following amendment for clarification is recommended, --said [method] retroinfusing further comprises using depot means--. The method doesn't use the depot means, the step of retroinfusing does.

When referring to limitations previously recited, it is proper to use the article --the-- instead of "a" or "an". In claim 5, the specification teaches that the invention is directed to methods of applying stress through the application of pressure, energy or chemical stress in a well to lead to its disruption. Hence, for consistency with the teaching with the application, "a

wall of said vessel" should be --the wall of said vessel-- to reflect the recitation in claim 1 "to disrupt a wall of said vessel". Similar amendment to claim 11, 13, 14, 16, 17, 19, 36, 39, 41, 43, 45, 47, 49, 50, 52, 53, 55, 57, 58, 60, 71, 80, 81, 83 to recite --the wall of said vessel (vein)-- is recommended.

In claim 7, accuracy is increased by reciting, --wherein said stress is a mechanical stress exerted on the wall of said vessel--. Similarly in claims 9, 57, 58, 68, 69, 80, 81 and 92, it would be remedial to recite, --wherein said conditions comprise a pressure sufficient to--. It would be remedial to amend claim 43 similarly to recite -- wherein said conditions comprise a pressure sufficient to produce the mechanical stress on the wall of said vessel-- and in claim 45, --wherein the pressure produces a mechanical stress on the wall of said vessel--.

Claims 31, 34, 62, 66, 73, 77, 85, 89, 96 and 100 recite, "wherein said retroinfusion comprises disrupting venous branches upstream of the site of administration for said agent to enter an interstitial space of said host through the disruptive passageways in the venous branches". Quite simply the claims are actually drawn to --wherein said vascular vessel is a venous branch upstream of the site of administration--. It would be remedial to amend the claims to recite so.

In claim 44 and 90, the recitation in line 3, "retroinfusing a fluid" does not indicate that the fluid comprises the agent. Hence, it would be remedial to recite --a fluid comprising the agent--.

Claim 7 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 3, claim 19 of claim 16 and claim 60 of 56. When two claims in an application are duplicates or

else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). The specification teaches that mechanical stress is the outcome of application of pressure or energy and hence inherently the application of pressure to produce disruptive passageways will result in the mechanical stress recited in claim 7. Similarly, claim 45 is a duplicate of claim 44.

Claim 11 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 8. Claim 11 recites that the method further comprises producing inflammation in a wall of the vein. However, the specification teaches that inflammation is a natural consequence of the stress on the vessel wall. Hence, producing inflammation does not require any steps from the practitioner but is inherent in the recited method steps. Similarly, claim 19 is objected for being a substantial duplicate of claim 16. Similarly, claim 47 is objected for being a substantial duplicate of claim 44. Similarly, claim 55 is objected for being a substantial duplicate of claim 52. Similarly, claim 60 is objected for being a substantial duplicate of claim 56. Similarly, claim 83 is objected for being a substantial duplicate of claim 78.

Claim 14 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 9. Claim 14 recites that that the wall is disrupted but claim 9 recites that the method comprises retroinfusion under conditions where the wall of the vein is disrupted. Hence, as set forth in claim 9, the vein is already disrupted. Claim 17 recites that that the wall is disrupted but claim 15 recites that the method comprises retroinfusion under conditions to produce a disruption and disruptive passageways in the wall of the vein. Disruptive passageways require that the wall is disrupted, hence, the recitation in claim 17 is a duplication of claim 15. Similarly, claim 50 is

objected for being a substantial duplicate of claim 45. Similarly, claim 53 is objected for being a substantial duplicate of claim 51. Similarly, claim 58 is objected for being a substantial duplicate of claim 56. Similarly, claim 92 is objected for being a substantial duplicate of claim 90.

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-104 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising balloon occlusion with retroinfusing a flowable formulation of said agent or a fluid delivery vehicle thereof or a fluid comprising the agent into a vascular vessel sufficient to disrupt and/or distend the vessel application of pressure sufficient to disrupt and/or distend the vessel, does not reasonably provide enablement for any other embodiment.

Claims 25-26 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method wherein retroinfusion is performed at 50 mm Hg, 50 mm Hg or 1000 mm HG, does not reasonably provide enablement for any other embodiment.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a

conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

The instant claims are drawn to a method of providing localized administration of an agent to a target site wherein the method involves transfer or infusion of the agent to the interstitial space proximal to a target site. The method comprises administration of the agent by retrograde transport into a vessel wherein the vessel is proximal to a target interstitial space. Claims 1-7, 15-19, 20-36 and 44-55 are drawn to methods of administering an active agent to a host wherein the method comprises retroinfusing a fluid comprising the agent, a flowable formulation of said agent or a fluid delivery vehicle thereof into a vascular vessel *under pressure sufficient* to disrupt a wall. Claims 8, 10-14, 37-40, 42, 56, 59-66, 78, 81-89, 101 and 103 recite that the method is performed *under conditions sufficient for the fluid to mechanically stress a wall*. Several claims i.e. claim 41, 56 and 78 "further comprise" the administration of energy. Claims 67, 70-77, 90, 91, 93-100, 102 and 104 recite that retroinfusion is performed *under conditions* wherein the vessel experiences stress, distends and then disrupts which results in the production of disruptive passageways through which the agent enters the interstitial space. The recitation "under conditions" particularly when the function of producing mechanical stress or even when use of pressure is present is broad and undefined. As such, the claims are drawn to a broad number of undefined conditions required to produce a specific function; to distend and/or disrupt the wall of a vessel proximal to a target site to result in the production of disruptive passageways such that an agent can enter the proximal interstitial space.

The instant invention is directed to, methods in which, "the agent is administered to the host in combination with the production of vascular stress at the site of administration, where the vascular tissue stress is sufficient to provide for transport of the agent from the vascular site of deposition into the target interstitial space. In a preferred embodiment, the agent is retroinfused at a pressure sufficient to provide for mechanical stress on the vessel proximal to the target interstitial space." Hence, mechanical or vascular stress is the product of an action wherein the "vascular wall stress may be produced in a number of different ways, where such ways include physical stress, chemical stress, combinations thereof, and the like. In many embodiments, the production of stress produces inflammation at the vascular site of deposition and proximal thereto, where the inflammation is desired and provides for enhanced activity of the active agent upon reaching the target interstitial space". The "stress may be produced in the vessel wall using a single means or using a combination of means, e.g. a physical means and a chemical means. Physical means of producing stress in the vasculature include pressure means, application of external energy, etc, where chemical means of producing stress in the vasculature include chemical inflammatory agents, etc. Representative physical and chemical means of producing stress in the vasculature that may be employed in the subject methods are now described in greater detail below (bridging ¶, col 4-5)". The specification continues that mechanical stress is placed on the wall, however, this mechanical stress is the product of 1) preferable a high-pressure environment such as resulting from occlusion of the vessel with fluid introduced at elevated pressure 2) application of energy 3) chemical stress. These components and conditions are not defined in the specification except by means of exemplification. Example 1 and 2 teaches disruption of the vessel walls by pressure during retrograde administration. The

disclosed method in example 1 involves balloon occlusion coupled with injection performed at hyperbaric pressure i.e. 5-30 mm Hg. In this example, the fluid is applied to produce the internal pressure sufficient to disrupt the vascular wall. Though not controlling, the lack of working examples, is, nevertheless, a factor to be considered in a case involving both physiological activity and an undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. Ex parte Sudilovsky, 21 USPQ2d 1702, 1705 (BPAI 1991); In re Novak, 134 USPA 335 (CCPA 1962); In re Fouche, 169 USPQ 429 (CCPA 1971).

In this case, applicants recite a number of broad and undefined parameters that are necessary to cause disruptive passageways in the vessel. While the specification teaches that disruption can be caused by physical, chemical and energy means, the parameters defining these conditions are not made. . In this case, the fine line between causing disruptive passageways and from causing harm is unclear. Furthermore, it is not clear that guidance for demonstrating the fine line is possible to be found in the art. Case law has established that ' (t)o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation.'" In re Wright 990 F.2d 1557, 1561. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that ' (t)he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art" The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the

art. The more that is known in the prior art about the nature of the invention, how to make and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order for it to be enabling.

In the case where the claims require distention as well as disruption without corresponding means to do so (claims 67, 70-77, 90, 91, 93-100, 102 amd 104, the specification specifically describes only a single condition wherein " the pressure is sufficient to result in distention of the vessel, whereby distention of the vessel is meant expansion of the vessel such that the cell wall in the region of fluid administration is stretched. Where distention is employed in the subject methods, the volume of the vascular deposition site bounded by the vessel walls typically increases in many embodiments by a factor of at least about 100%. Distention of the vessel walls results in increased permeability of the vessel walls to the active agent, where the permeability increases by a factor of at least about 5 and usually by a factor of at least about 10%". The specification does not disclose any other methods that lead to distention of the vessel walls. It is noted that claims directed to distention of the vessel walls following the application of pressure are also claimed in a variety of other claims. Furthermore, claims 25-26 are drawn to conditions of retroinfusion performed at pressures of *at least* 50, 60 or 1000 mm Hg. As well, the recitation that the pressures are "at least" is similarly broad. By recitation of "at least", there is simply no upper limit. This cannot be as excessive pressure would cause permanent damage to the host as well as the targeted vascular vessel.

The invention recites use of a broad group of conditions as well as pressures to be used. Given the unpredictability of the art, the lack of adequate working examples and the lack of guidance provided by applicants, the skilled artisan would have to have conducted undue, unpredictable experimentation to identify amongst any number of conditions or any number of pressure levels that are at least 50, 60 or 1000 mm Hg.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 7-11, 13-19, 21-23, 29-39, 43-47 and 49-100 stand rejected under 35 U.S.C. 102(e) as being anticipated by Wolff et al (US 6,867,196; see entire document). **Upon reconsideration, the above art rejection has been reinstated. Arguments are addressed below.**

Wolff et al teach methods of delivering nucleic acid to cardiac tissue using a catheter (forming a channel) into cardiac tissue from a vessel (vein or artery, see e.g. col 8, line 10-19), The instant specification defines interstitial space as the region or tissue beyond the wall of the vascular site or beyond the intimal space (see e.g. bridging paragraph col 3-4). The method involves a retrograde approach with increased permeability of the vessels as recited in claims 1, 2, 8, 10, 13, 14, 21-23, 30 and 36-38 (see e.g. abstract, col 9, line 4-27 and col 11, line 1-65).

Permeability of the vessel is increased by intravascular hydrostatic pressure by the fluid delivery vehicle as recited in claims 15-18, 44, 46, 49-53 (see e.g. col 11, line 1-55), this increased permeability results in channels to the heart and is equal to a disruption in the vessel such that agent is delivered to the interstitial space. Stress is placed proximal to the interstitial space and can be chemical (see e.g. col 11, line 34-54) as recited in claims 3, 29 and 39. As well, the stress can also be mechanical as it is generated by clamping (see e.g. col 11, line 1-21) as recited in claims 7, 9, 43, 45, 56-59, 61, 68, 78-82 and 84. A catheter is used that has an occlusion device downstream of the site of administration of the agent (see e.g. figure 3) as recited in claims 32, 34, 63, 65, 74, 76, 86, 88, 97 and 99. As demonstrated in figure 3 and figure 4, the catheter comprises an occlusion device that is upstream and downstream of the site of administration. The specification does not define venous (venous) branches. During prosecution, claims must be interpreted as broadly as their terms reasonably allow. Thus, as depicted in figure 4, the catheter would place an occlusion device such that at least one upstream branch of the vessel can be occluded as recited in claims 33, 64, 75, 87 and 98. This should necessarily result in disruption through increased permeability of the venous branches upstream of the vessel as recited in claims 31, 35, 62, 66, 73, 77, 85, 89, 96 and 100. Finally, Wolff et al teach that nucleic acids encoding cytokines can be delivered. Many cytokines are responsible for producing inflammatory responses. Thus it would be inherent that administration of cytokines would lead to production of inflammation in the vessels as recited in claims 11, 19, 47, 55, 60, 71, 83 and 94.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-24 and 28-104 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US 6,867,196; see entire document) in view of Makower et al (US 2002/0179098; see entire document). **Upon reconsideration, the above art rejection has been reinstated. Arguments are addressed below.**

Applicants claim a method of locally administering an active agent comprising retroinfusing an agent into a vascular vessel under conditions sufficient for an agent or fluid delivery vehicle to produce a disruption which method further comprises administration of energy to the vessel. As well, the agent is delivered to a myocardial space and the agent can be cells or dye or imaging agents, the vessel can be a venous branch.

The teachings of Wolff et al are described above and are applied as before except;

Wolff et al do not teach that the method further comprises administration of energy to the vessel, the agent is delivered to a myocardial space and the agent can be cells or dye or imaging agents.

Makower et al teach a method of locally administering an active agent such as xenograft tissue (which inherently comprise cells, peptides, proteins and nucleic acids) signal emitting targets or radiological imaging material, imaging means or dyes (see e.g. paragraph 0012, 0097, 0109 and 0161) in which the agent is retroinfused into a vascular vessel such as a vein under

conditions sufficient to disrupt the vein such that the agent enters interstitial space such as the myocardial space as recited in claims 6, 12, 20, 24, 42 and 48 (see e.g. paragraph 0097). The method further comprises administration of energy to the vein such as heat as recited in claim 5, 28, 41, 56-59, 61-70, 71-82, 84-93 and 95-104 (see e.g. paragraph 0114, claims 75 and 76). Heat is used to keep the non-stented passageways open and to prevent scarring as well as a depot means carrying the cells as recited in claim 4 and 40 (see e.g. paragraph 0169).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to locally deliver to the myocardial beds an agent by retroinfusion such that a disruption results in the vascular vessel to the interstitial space as taught by Wolffe et al in which the disruption is produced in the myocardial interstitial space and to then apply energy such as heat in the method as taught by Makower et al because Wolffe et al teach that it is within the ordinary skill of the art to retroinfuse agents into a vascular vessel such that a passageway to the interstitial space is created and because Makower et al teach that it is within the ordinary skill of the art to deliver agents to the myocardial space following retroinfusion and to apply energy such as heat during the method. One would have been motivated to do so in order to receive the expected benefit of delivery to the myocardial space to treat coronary artery disease and for revascularization in which a passageway to the myocardial interstitial space has been generated using xenograft tissue and has been treated with heat to decrease incidence of scarring and incidence of closure. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 1 and 25-27 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Wolff et al (US 6,867,196; see entire document). **Upon reconsideration, the above art rejection has been reinstated. Arguments are addressed below.**

Applicants claim a method of locally administering an active agent to a host by retroinfusing said agent into the vessel under pressure of at least 50mm Hg, 60 mm Hg and 1000 mm Hg.

The teachings of Wolff et al are described above and are applied as before except;

Wolff et al do not teach that the pressure used during retroinfusion is at least 50mm Hg, 60mm Hg and 1000mm Hg.

It would have been obvious to someone of skill in the art to utilize pressure of at least 50mm Hg, 60 mm Hg and 1000 mm Hg in the method of Wolff et al given that the identification of these pressures would be required to optimize the hydrostatic pressure to permeabilize or disrupt the vessels for deliverance of the agents. A person of skill in the art would have been motivated to optimize these conditions to best utilize the methods of Wolff et al for deliverance of agents to interstitial spaces. The MPEP teaches "Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." see also Peterson, 315 F.3d at 1330, 65 USPQ2d at 1382 ("The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages"). Given the teachings of the cited art and the

level of skill of the ordinary skilled artisan at the time of the applicant's invention, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Response to Argument

Applicants traverse the claim rejections under 35 U.S.C. 102 and 103 on pages 24-27 of the amendment filed 4/28/08. Applicants' arguments filed 10/9/07 have been fully considered but they are not persuasive. Specifically, applicants argue that Wolff teaches only enhanced delivery through natural channels not through "disruptive channels". Wolff et al teach that gene transfer is increased by raising the osmolarity of an injection. Wolff et al do not know the method of enhanced extravasation but suggest that it maybe through the destruction of tight junctions or increase of pore size or by large pores. However, it is clear that the increase is due to fluid leakage (see col 5, line 44-67). Similar comment is made in col 6, line 14-21). As noted above, the claims simply require retroinfusing an agent *under pressure sufficient* to disrupt a wall, *under conditions sufficient for the fluid to mechanically stress a wall, under conditions.* Wolff et al teaches this method and given the overlapping nature of the claims, one would expect the method of Wolff et al to lead to disruptive passageways. Wolff teaches that permeability of a vessel is increased by increasing the intravascular hydrostatic pressure combined with obstructing or impeding the outflow of injected fluid (see col 11). It is not clear what would lead two similar methods to distinct outcomes. Because the Office does not have the facilities for examining and comparing the applicant's product with the products of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed products and the

products of the prior art (e.g. that the products of the prior art do not possess the same material structural and functional characteristics of the claimed product). See in re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977). Absent evidence to the contrary, a method of retroinfusing an agent into a vessel under conditions such as hydrostatic pressure coupled with balloon occlusion would lead naturally and inherently to disruptive passageways forming in the vessel walls.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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